FINAL TECHNICAL REPORT

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During the tenure of this Agreement, we have used 2 approaches to study the effects of hormones involved in volume and pressure control on physiological variables. In the first (Darlington et al. (1989) Paraventricular stimulation with glutamate elicits bradycardia and pituitary responses. Am. J. Physiol. 256:R112-R119) the effects of electrical and glutamate stimulation of the PVN were compared on blood pressure, heart rate and endocrine responses. The effects of both stimuli were specific to a locus in the parvicellular PVN, and did not occur when the electrode or injection cannula was outside this region of brain. Similar results to those with glutamate were found using norepinephrine as the stimulating agent. Dose-response curves showed threshold responses when NE at 10^{-7} M was injected. Our subsequent attempts to perform such maneuvers in awake, behaving rats were failures. We have not yet found a means of controlling the injection of the very small (20 nl) volumes required for specificity in these studies.

The second sets of studies which were supported by this agreement were those on the effects of feeding and fasting on suvival after hemorrhage in adrenalectomized rats. These studies began with the finding that replacement quantities ofcorticosterone only produced small effects on vascular responses to catecholamines in bilaterally adrenalectomized rats (Darlington et al. (1989) Vascular responsiveness in adrenalectomized rats with corticosterone replacement. Am J. Physiol. 256:H1274-1281) although overreplacement with corticosterone caused hypertension. With this finding in hand, we next studied the effects of adrenalectomy on hormonal responses to the stimuli of hemorrhage and insulin-induced hypoglycemia (Darlington et al. (1989) Potentiation of hormonal responses to hemorrhage and fasting, but not hypoglycemia in conscious adrenalectomized rats. Endocrinology 125:1398-1406). There were clearly elevated resting levels and

potentiated responses in the hormones involved in the regulation of blood pressure and volume in the adrenalectomized rats, and 3/7 adrenalectomized animals did not survive the 24 h period after hemorrhage. Nonetheless, the adrenalectomized rats were able to restore pressure and volume after hemorrhage similarly to intact rats.

Because a check of our daily records revealed that the 3 rats that died had lost weight during the experiment, we next tested the effect of fasting on the capacity of adrenalectomized rats to survive a standard hemorrhage. The experiment used a square design with fed and fasted sham-adrenalectomized and adrenalectomized rats exposed to hemorrhage. 100% of the fasted adrenalectomized rats died during the hemorrhage period whereas all of the animals in the other 3 groups lived (Darlington et al. (1990) Fed but not fasted adrenalectomized rats survive the stress of hemorrhage and hypovolemia. Endocrinology 127:759-765). Mean arterial pressure and plasma glucose fell paripassu in the animals that would die in the subsequent period.

To distinguish between the fall in pressure and glucose as lethal, a final study was done in which fasted intact and adrenalectomized rats were exposed to hemorrhage. Four groups of adrenalectomized rats were studied: saline infused, glucose infused, acutely or chronically replaced with corticosterone. Only corticosterone caused the adrenalectomized rats to survive hemorrhage (Darlington et al. (1990) Corticosterone but not glucose treatment enables fasted adrenalectomized rats to survive moderate hemorrhage. Endocrinology 127:766-772). The results of these studies clearly distinguished the decrease in pressure rather than glucose as a cause of death, and suggested that there was a marked decrease in liver blood flow mediated by extraordinarily high vasopressin and AII levels in the dying rats.

In our final experiments, Dr. Darlington returned from his present position at the University of Md. to SF for one month, last August (1990), to test the hypotheses that blocking the action of AVP or catecholamines would allow rats to survive, and to measure liver blood flow using the microsphere technique as employed in the Rudolph-Heymann lab in the CVRI at UCSF. During this month Dr. Darlington prepared 100 rats with indwelling cannulae and adrenalectomized them. However, 67% of the ADX rats died with no further manipulations performed on them; consequently, we have only the most preliminary data from these studies and will have to try them again. With more time, and more failed experiments and animal

deaths, it turned out that our rat rooms were being bombarded by drilling and other construction-related noise going on around us. Since May 1990, we have not been able to trust any experimental results produced in the lab, and we are in the process of repeating the year's work.